SHORT REPORT

Morphine versus remifentanil for intubating preterm neonates

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A double-blind, randomised controlled study was conducted to evaluate the intubation conditions in 20 preterm neonates following the use of either morphine or remifentanil as premedication. The findings suggest that the overall intubation conditions were significantly better (p = 0.0034) in the remifentanil group than in the morphine group. No severe complications were observed in either group.

Endotracheal intubation of preterm neonates forms a major part of routine practice in the neonatal intensive care unit (NICU). This procedure is associated with physiological and biochemical responses, and premedication (sedation and analgesia) seems to improve physiological stability and decrease the time taken for and the level of difficulty of the procedure.[1] Morphine has been used for several years in most NICUs with apparent safety and efficacy, and midazolam is given for sedation.[2 3] However, morphine has several limitations, the main one being its delayed onset of action, which makes the drug unsuitable for premedication.[1 2] In this setting, remifentanil has theoretical and practical advantages over other sedative drugs, making it appropriate for noxious procedures such as intubation and ventilation.[4]

The aim of our randomised double-blind study was to compare the intubation conditions achieved following sedation with remifentanil and morphine in preterm neonates with respiratory distress syndrome (RDS).

PATIENTS AND METHODS

Our study population included 20 preterm neonates (28–34 weeks' gestation) admitted to a single tertiary NICU, who required elective tracheal intubation to treat respiratory failure due to RDS. The ethics committee of our institution approved the study, and informed consent was obtained from parents of all selected neonates. Neonates were excluded from the study if they had major congenital malformations, birth weight less than 1000 g, previous or concurrent use of opioids or haemodynamic instability before intubation.

Following enrolment the neonates were randomised sequentially, using a random numbers table, to receive an intravenous bolus injection over 1 min of either morphine 150 μg/kg and midazolam 200 μg/kg or remifentanil 1 μg/kg and midazolam 200 μg/kg. A single pharmacist was responsible for allocating each neonate in the randomised treatment group, and she also ensured that the two preparations could not be differentiated.

The neonates were preoxygenated with 100% oxygen and a monitor (Dixtal 2010; Dixtal Collaborative Evolution, São Paulo, Brazil) recorded the heart rate, blood pressure and oxygen saturation (SaO_2). A single paediatric anaesthetist, who was blinded to the study protocol, carried out all intubations and classified the intubation conditions as poor, good or excellent.[5] The intubation conditions were scored using a four-point scale and the variables assessed were: ease of laryngoscopy, position of the vocal cords, coughing, jaw relaxation and movement of the limbs.[5]

The blood pressure, heart rate and Spo_2 were recorded before and during the first 10 min after the intubation. Pain and stress were assessed before and after the intubation using the neonatal infant pain scale (NIPS)[6] and the Comfort score,[7] respectively. These include physiological and behavioural measures.

Statistical analysis

We analysed the data using Fisher's exact test and the Mann–Whitney U test for non-parametric data. One-way analysis of variance for repeated measures was used for parametric data followed by post hoc multiple comparisons using Student–Newman–Keuls test. We also calculated the odds ratios to assess the magnitude of the differences between the groups regarding the intubation conditions. A p value of <0.05 was considered significant.

RESULTS

An equal number of neonates were randomised to sedation with remifentanil (n = 10) and morphine (n = 10). The two groups had similar demographic characteristics, none of the neonates had acute asphyxia and none was receiving non-opioid sedation or was born to a mother receiving magnesium sulphate. All neonates had had continuous positive airways pressure treatment before intubation with similar ventilatory parameters and degree of RDS. Each tracheal intubation attempt required less than 30 s.

Table 1 shows that excellent intubation conditions were not achieved in any neonate in the morphine group compared with six neonates (60%) in the remifentanil infusion group (p = 0.0034). A second attempt to intubate was only required in neonates infused with morphine (n = 4). The probability of having excellent intubation conditions, easy laryngoscopy, opened vocal cords and a completed relaxed jaw was 24 (95% CI 1.1 to 505.2), 12 (95% CI to 1.1–128.8), 32 (95% CI 2.4 to 427.7) and 20 (95% CI 1.7 to 238.6) times higher, respectively, in the remifentanil group than in the morphine group (tables 1 and 2).

We did not find any significant differences between the groups regarding pain and stress levels before and after the intubation using the NIPS scale and the Comfort score (data not shown). There were also no differences between the groups with regard to the haemodynamic variables (blood pressure

Table 1 Comparison of the quality of intubation achieved in neonates pre-infused with morphine and remifentanil[5]

	Excellent	Good	Poor	Total
Morphine	0	6	4	10
Remifentanil	6	4	0	10
Total	6	10	4	20

p = 0.0034 (Fisher's exact test).

Abbreviations: NICU, neonatal intensive care unit; NIPS, neonatal infant pain scale; RDS, respiratory distress syndrome

Table 2 Assessment on a four-point scale of intubation conditions achieved with pre-infusion with remifentanil and morphine in preterm neonates[5]

Intubation condition	No. of neonates		
	Morphine	Remifentanil	p Value
Laryngoscopy			
Score 1	5	10	
Score 2	1	0	0.033*
Score 3	4	0	
Score 4	0	0	
Vocal cords			
Score 1	1	8	
Score 2	8	2	0.006*
Score 3	1	0	
Score 4	0	0	
Coughing			
Score 1	7	10	
Score 2	2	0	0.211
Score 3	1	0	
Score 4	0	0	
Jaw relaxation			
Score 1	3	10	
Score 2	6	0	0.003*
Score 3	1	0	
Score 4	0	0	
Limb movement			
Score 1	5	8	
Score 2	3	2	0.303
Score 3	0	0	
Score 4	2	0	

*$p<0.05$ (Fisher's exact test).

and heart rate) during the first 10 min after intubation (data not shown). No severe adverse effects, such as chest wall rigidity, rash, significant hypotension, bradycardia, arrhythmia or hypoxaemia were observed after infusion of either drug.

DISCUSSION

Awake intubation in neonates is associated with pain and adverse physiological responses, such as hypoxia, bradycardia, systemic and intracranial hypertension, which may lead to intraventricular haemorrhage and/or periventricular leukomalacia, as well as prolongation of the procedure and the need for multiple attempts.[1 2] However, premedication has been shown to attenuate these deleterious effects.[1 2] The present study compared the intubation conditions in preterm neonates with RDS, using remifentanil or morphine as premedication.

We found that the intubations conditions in the remifentanil group were significantly better than in the morphine group. Indeed, the probability of having excellent intubation conditions was 24 times higher with remifentanil than with morphine. In addition, we observed that 4/10 neonates pretreated with morphine required a second intubation attempt. On the other hand, all patients pretreated with remifentanil were intubated at the first attempt.

The doses of remifentanil and morphine that we used in the present study were based on other studies.[4 8 9] The success of an intubation is directly related to the moment of the tracheal intubation and time of the peak plasma concentration of the drug used as premedication.[8] In this regard even if morphine's actions begin in 5 min, its $T_{1/2}Ke0$ (half-time for equilibration between plasma and effect compartment) is 30 min.[9] This could be too long for intubation; because of the delay in achieving the peak concentration of morphine, there could be insufficient relaxation and airway exposure at the time of laryngoscopy and intubation. In contrast, remifentanil has a rapid onset of action with a calculated $T_{1/2}Ke0$ for analgesia of 1.3 min (1.0–1.5).[8] In the present study, the intubation was done 120 s after an intravenous bolus administration of midazolam and 150 s after the opioid (morphine or remifentanil) was administered. This means that the procedure was carried out at the peak of action of remifentanil but at a lower plasma concentration of morphine. These pharmacological properties of remifentanil and morphine may explain the differences in intubation conditions between the two groups in the present study. A similar dose–response relationship of remifentanil for tracheal intubation has been found in healthy full-term neonates and in children with a rate of successful intubation of about 80%.[8]

With regard to pain, both drugs performed well, considering the differences between the scores of pain and stress before and after the intubation; in addition, there were no differences between the groups with regard to pain. There were also no differences between the groups with regard to the haemodynamic variables (blood pressure and heart rate). Muscle rigidity has been observed in 11–32% of neonates with target concentrations of remifentanil between 2 ng/ml and 16 ng/ml.[10] However, it is noteworthy that none of our neonates had this complication, probably because we used a slower rate of administration of remifentanil.

The small sample size of our study may be of concern. However, a post hoc power calculation using the observed sample sizes, the qualitative and quantitative assessment of intubation conditions, and a type 1 error rate of 5% show that our study had a statistical power of 83%, so that the differences observed in the intubation conditions were not due to chance alone (nQuerry Advisor 4.0 Statistical solutions, Saugus, MA, USA). Thus although limited in size, our strict inclusion criteria and use of randomisation have provided important preliminary information for future investigations. Indeed, further studies are obviously necessary to confirm our data.

In conclusion, our findings suggest that remifentanil seems to be a better option than morphine as premedication for intubation in preterm neonates.

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